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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,996	02/08/2002	Ruiping Liu	MEMORY-2	9946
24980	7590	12/22/2006	EXAMINER	
MILLEN, WHITE, ZELANO & BRANIGAN, PC			BERCH, MARK L	
2200 CLARENDON BLVD			ART UNIT	PAPER NUMBER
SUITE 1400			1624	
ARLINGTON, VA 22201				
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE		DELIVERY MODE	
3 MONTHS	12/22/2006		PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/067,996	LIU ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 November 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,3-36,60,61,71-74,77,80 and 94-114 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,3-36,60,61,71-74,77,80 and 94-114 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/13/2006</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/27/2006 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 16, 18-22, 24-29, 60-61, 73, 94, 97, 101-114 are rejected under 35 U.S.C. 103(a) as being obvious over JP 2000-072773.

See table 1, compound 5, which has R1 as methyl, and R2 has a 1,2,3,4-tetrahydroquinolinyl-2-yl-methyl. This species is removed by proviso (a). But the 3-yl or 4-yl isomer would render the claims obvious. It is well established that position isomers are *prima facie* structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt*, 208 USPQ 343, 349; *In re*

Mehta, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullerot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 247, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154.

For example, “Position isomerism has been used as a tool to obtain new and useful drugs” (Englehardt) and “Position isomerism is a fact of close structural similarity” (Mehta, emphasis in the original). Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 “Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness”; one of those listed is “adjacent homologues and structural isomers”. Position isomers are the basic form of close “structural isomers.” Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states “a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds.” Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, “Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds ... a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para).” See also MPEP 2144.09, second paragraph.

Claims 1, 3-4, 6, 10, 16-17, 21, 27-32 and 60-61, 68, 70, 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley(1990) i.e. Reference 4 of 11/6/2002 submission or Reference A34 of the 4/15/2002 IDS.

Compound 2 is an antiviral against rhinovirus type 1B. The species is excluded by proviso, but this methyl compound is a homolog of the corresponding ethyl compound, i.e. compound where R1 in the claims is ethyl. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a *prima facie* case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 247; *Ex parte Henkel*, 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *In re Herr*, 134 USPQ 176; *Ex parte Dibella*, 157 USPQ 59; *In re Zickendraht*, 138 USPQ 22; *Ex Parte Fischer*, 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39; *In re Bowers and Orr*, 149 USPQ 570. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or

isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds.” Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, “Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.” See also MPEP 2144.09, second paragraph. Note that Rhinovirus always causes inflammation.

Species 11, 8, 9, 12, 14, 15, 17, 18, 21 and 22., having the cyclopropyl and 9-methyl benzyl, no longer renders the claim 1 (or claim 98) obvious because of the expanded (b) proviso. These species would still be relevant to claim 68 and 70 because the amendments to the claim 68 provisos are not relevant to this species, and the claim 70 provisos were not amended.

The traverse is unpersuasive. With regard to compound 2, the remarks state, “In the numerous cases cited by the Examiner, the compounds involved differed by one or two methyl groups wherein the alkyl groups in question were substituents attached to a carbon ring atom or a carbon atom of a chain.” Exactly that situation applies here, for the “or a carbon atom of a chain” branch of the above sentence. The carbon chain of methyl has an additional methyl group attached to extend the chain from methyl to ethyl. It is not seen what difference it makes what the entire chain is ultimately attached to. In every one of the cases cited, the extra methyl group is attached to something different. Each case has its own structure. However, the concept of a homolog is independent of what the alkyl chain is

ultimately connected to. Applicants have not presented any definition of homolog that makes it dependent on what the alkyl chain is attached to.

Claims 1, 3, 6, 10, 16-17, 21, 27-32, 35, 60-61, 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bourguignon i.e. Reference 5 of 11/6/2002 submission or Reference A37 of the 4/15/2002 IDS.

Compound 6i corresponds to R2=benzyl, R1=H, and is excluded by proviso. Even with the rewritten third proviso, the compound is still a homolog. However, it renders the corresponding homolog where R2= dimethyl-benzyl obvious, for reasons set forth previously. The two methyl groups could be on the alpha-carbon, one on the alpha and one on the ring, or both on the ring. It also renders obvious the chain homolog where R2 is phenethyl, i.e. $(CH_2)_3\text{-Phenyl}$ rather than $(CH_2)_1\text{-Phenyl}$ (note that while $(CH_2)_2\text{-Phenyl}$ was excluded, $(CH_2)_3\text{-Phenyl}$ was not).

The traverse on the chain homolog issue is not persuasive. It is agreed that the prior art $Ph(CH_2)_1\text{-}$ and the claims $Ph(CH_2)_3\text{-}$ differ by the insertion of $-(CH_2)_2\text{-}$. When dealing with a chain between two groups, it has been established that two carbon differences are still obvious. *Ex parte Ruddy*, 121 USPQ 427 specifically has an extra has a C_2H_4 link between a phenyl ring and a heterocyclic ring, exactly as here in the $(CH_2)_3\text{-Phenyl}$ situation. In addition, applicants should also note *Ex parte NATHAN*, 121 USPQ 349, cited previously. This case also featured the insertion of $-(CH_2)_2\text{-}$, this time between a heterocyclic ring and a carboxy group. If applicants disagree, they are invited to state how this situation differs from *Ruddy* and *Nathan*.

Compound 6d, 6k, and 6l no longer render obvious the claims because of the expanded first proviso.

Claims 1, 3-6, 8, 15-31, 60-61, 94-95, 97 and 100-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley(1997) i.e. Reference A38 of the 4/15/2002 IDS.

The compounds are antipsychotic agents. Compound 80 (see table 7) corresponds to R1=cyclopropyl, R2= -(CH₂)-cyclopropyl. This species is excluded by the expanded proviso b. However, it renders obvious the homolog compound where the two extra methyls appears on the methylene, i.e. -(C(CH₃)₂)-cyclopropyl. Such a homolog compound is structurally obvious for reasons set forth previously. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 247; *Ex parte Henkel*, 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *In re Herr*, 134 USPQ 176; *Ex parte Dibella*, 157 USPQ 59; *In re Zickendraht*, 138 USPQ 22; *Ex Parte Fischer*, 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39; *In re Bowers and Orr*, 149 USPQ 570. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore

chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." See also MPEP 2144.09, second paragraph.

In addition, the reference itself provides a motivation for this exact alteration. Table 6 deals with R1=cyclopropyl compounds, and this exact modification is shown. Note that compound 54 has the R2= -(CH₂)-cyclopropyl and compound 60 has the -(CHCH₃)-cyclopropyl. Compound 60 is twice as potent, which will motivate one of ordinary skill in the art to put an extra methyl --- or two extra methyl groups on that exact position in compound 80, as this teaching arises specifically in the context of R1=cyclopropyl compounds.

In addition, the expanded proviso b does not bar the compound R1=cyclopropyl, R2= -(CH₂)-cyclopropyl(CH₃), i.e. the compound where a methyl group is attached to the cyclopropyl. Note that the cycloalkylalkyl choice permits substitution by methyl.

In addition, the R2= -(CH₂)-cyclopropyl compound would render obvious the R2= -(CH₂)₃-cyclopropyl (i.e. cyclopropylpropyl) as a chain homolog. Note the previously cited *Ex parte Ruddy*, 121 USPQ 427 has a C₃ link unpatentable over a C₁ link, and *Ex parte Nathan*, 121 USPQ 349 which found the insertion of a C₂H₄ link obvious. In this regard, the circumstance is the same as in the Bourguignon rejection. Thus, claims 1, 4, 27-29, 60, 94 and 97 are considered obvious.

In addition, note species 49-52, 54, 56-70. These have R1 as alkyl, cycloalkyl-alkyl, or cycloalkyl and R2 as cycloalkyl, cycloalkyl-alkyl, alkyl, or alkyl with one C replaced by S. These species all lack the 2-CF₃ feature. However, the 2-CF₃ feature is specifically seen in compound 80. In fact, the reference provides specific motivation for such a modification, to add the 2-CF₃ feature. The table 7 comparison between compounds 54 and 80 shows that

attaching the 2-CF₃ group produces a 6-fold increase in oral potency. In fact, that 2-CF₃ compound is the most potent in the entire table. Thus, one is motivated to attach the 2-CF₃ group to obtain such an improvement. Accordingly, claims 1, 3-6, 8, 15-31, 60-61, 94-95, 97 and 100-114 are considered obvious.

The remarks filed with the RCE did not make any particular mention of this reference.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-36, 60-61, 71-74, 77, 80, 94-114 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-53, 62-67, 72-118 of copending Application No. 10845354. Although the conflicting claims are not identical, they are not patentably distinct from each other because of a lack of patentable distinction.

The claims in this case are drawn to compounds, compositions, and method of making; those of the daughter case are drawn to method of use. There is ordinarily no patentable distinction between compositions of matter and methods. Hence, in the absence of a Terminal Disclaimer, an obviousness-type Double Patenting rejection may be made. See *In re Boylan*, 157 USPQ 370 [The patent had a composition of matter and a method of making it; the application had the method of use]; *Ex parte MacAdams*, 206 USPQ 445 [The patent had a composition of matter; the application had the method of use]; *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline PLC*, 68 USPQ2d 1865 (CA FC 2003) [The earlier patent was drawn to method of use, the later three patents, held invalid in "Geneva II" were drawn to somewhat narrower versions of the composition of matter].

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3-36, 60-61, 71-74, 77, 80, 94-114 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-95 of copending Application No. 10636979. Although the conflicting claims are not identical, they are not patentably distinct from each other because the two cases heavily overlap.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

With regard to the ODP rejection over 10636996, applicants now state, "group is rendered obvious by a 6-dimethylamino. The rejection does not cite any case where a court held a monomethylamino and a dimethylamino to be adjacent homologs, nor does the rejection set forth any scientific definition that holds that monomethylamino and dimethylamino are adjacent homologs." While it is true that none of the cases have that exact monomethylamino-dimethylamino situation, the cases that are cited are certainly close enough to be applicable. The difference between the two is the replacement of a H sitting on a N with a methyl. That is exactly the situation of *In re Doebele*, 174 USPQ 158, *Ex parte Bluestone*, 135 USPQ 199, and *Ex parte Weston*, 121 USPQ 428 where this was not held to be a patentable distinction. One is a secondary amine, the other is a tertiary amine --- just as is the case here. As was stated in *Weston* "any chemist is readily aware of the difference between secondary and tertiary amines". The replacement of H with methyl on an amine was also the case in *In re Hoeksema*, 154 USPQ 169, although the difference there was between a primary and a secondary amine. The decision there explicitly called this a homolog situation. The court decision in *Doebele* referred to the examiner calling it a homolog, and the decision does not disagree with that description.

The examiner has thus cited four cases; applicants have given no reason why these should not be dispositive of the issue of the lack of patentable distinction between compounds which differ just by the replacement of H with methyl on a N.

However, the recent amendments in 10636996 removed the dimethylamino choice from all but claim 87, and that has an R2 substituent which is outside of claim 1 here, so that this rejection will be dropped and will remain so as long as that state of affairs

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Mark L. Berch
Primary Examiner
Art Unit 1624

12/15/06